(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 558 965 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
16.08.2000 Bulletin 2000/33

(21) Application number: **93102107.5**

(22) Date of filing: **11.02.1993**

(51) Int. Cl.[7]: **C08G 63/664**, A61L 29/00, A61L 31/00, A61L 17/00, A61L 2/08

(54) Reduced friction coatings for articles in contact with human or animal tissues

Überzugsmittel zur Verminderung der Reibung von Gegenständen in Kontakt mit menschlichen oder tierischen Geweben

Revêtements pour la réduction de la friction d'articles en contact avec des tissus humains ou animaux

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **02.03.1992 US 843053**

(43) Date of publication of application:
08.09.1993 Bulletin 1993/36

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Description

Background of the Invention

[0001] This invention relates to materials for medical or veterinary use that possess considerably improved properties with regard to friction.

[0002] Specifically, the present invention relates to a block copolymer for coating medical or surgical devices according to the preamble of claim 1.

[0003] Such materials may be produced from existing materials that possess suitable bulk properties, but inappropriate frictional properties. This invention also relates to a hydrophilic coating material that provides improved frictional properties.

[0004] In a particular aspect, the materials and method of this invention are useful for the fabrication of articles which contact the fluids or tissues of humans or animals.

[0005] In a medical procedure the facile movement of a surface with respect to tissue is important in reducing damage to both the material of the surface and to the tissue. Damage to tissue as a result of "tissue drag" causes inflammation and pain to the person or animal and leads to a longer recovery time. High friction between the surface material and blood may result in clotting and subsequent occlusion of a blood vessel, for example with indwelling catheters. Friction may also damage the material, thus rendering it ineffective or shortening its useful life. The problem of "tissue drag" has been of concern to the medical and veterinary professions for some time.

[0006] Although friction may be reduced by the use of lubricating oils, such liquids are weakly associated with the surface of the material and will be removed upon repeated rubbing of the surface against the tissue, as in multiple loop suturing. The toxicity of the oils and their breakdown products are a major concern. The surfaces of this invention are an improvement over the existing art which uses these lubricating oils.

[0007] A number of patents describe the use of non-absorbable hydrophilic or hydrogel coatings which provide lubrication when wet. The coatings are disadvantageous due to the complex coating methods described. The multiple components of these coatings would also present serious toxicology concerns.

[0008] The frictional properties of solid polymers, metals or ceramics are strongly dependent on the chemical composition of the material surface. The tissue drag of medical or veterinary materials is a result of interfacial forces between the material and the tissue, and as a result is also affected by the composition of the material surface. A number of techniques known in the art are designed to effect a chemical change in the surface of materials and thereby alter the frictional properties of the surface. These techniques include corona discharge, flame treatment, acid etching, etc.

[0009] The present invention will be illustrated with respect to elastomeric sutures. It should be understood, however, that this in no way limits the scope of the invention. The method of the invention is equally useful for imparting low friction surfaces to catheters, pacemaker leads and other medical or veterinary products, as defined in the claims.

[0010] The utility of this invention is illustrated by the following analysis of suture properties as related to continuous vascular anastomosis: "The use of monofilament polypropylene (PROLENE®-Ethicon) or monofilament polybutester (NOVAFIL®-Davis and Geck) makes accurate anastomosis feasible, by allowing a number of suture loops to be placed with good vision prior to tightening of the suture to approximate the edges to be joined. Monofilament polypropylene (PROLENE®) has long given excellent results in our experience. The particular advantage of this material is the ease with which the suture will pull through the tissues with minimal tissue drag. PROLENE® is relatively stiff and even in fine anastomoses with 7/0 PROLENE® there may be distortion of the anastomotic line. The recently available monofilament polybutester (NOVAFIL®) has given excellent results in our practice and has shown improved handling characteristics - less 'memory' and stiffness making it an easier material to use. The suture is slightly elastic - this may have theoretical advantages in a pliant small vessel - and the reduced stiffness results in less distortion of fine anastomotic lines. When using the open technique, it is important to pull the suture tight after every two or three loops to avoid having loose loops in the anastomosis. This overcomes any problem that may be experienced with increased tissue resistance when using NOVAFIL®." (From "Surgery of Coronary Artery Disease", D. J. Wheatley, ed., The C.V. Mosby Co., St. Louis, 1986.)

[0011] In certain procedures the surgeon, rather than tightening each suture loop individually may place multiple loose loops of suture in the tissue and then tighten the loops by pulling one or both ends (see Figure 1). In vascular and other tissues, the two ends of tissue may be pulled together by pulling the suture ends, which is often referred to as the "parachute technique." The parachute technique is commonly used in suturing vascular tissue. Polypropylene is the most common suture material used for this technique. Techniques of this sort are advantageous since they provide benefits to the patient. Suture placement is more accurate since each end of tissue is better visualized. The technique is also faster and reduces the time until blood flow is restored.

[0012] Good slip of sutures through tissues is critical for applications such as vascular surgery. However, some currently available sutures such as polybutester tend to exhibit "stick-slip" behavior as they are pulled through tissue.

These surfaces may initially move smoothly, but they then stick to the tissue and have to be pulled harder in order to continue the suturing process. The resulting oscillatory force may damage delicate vascular tissue. Sutures made from materials such as polypropylene do not show stick-slip behavior to the same extent as polybutester, but they are not sufficiently elastic for surgery on delicate tissue. A particular aspect of this invention overcomes the deficiencies of the prior art by disclosing sutures which are highly elastic and have a low friction surface that avoids stick-slip behavior.

[0013] There is an advantage in using elastomeric sutures such as polybutester in cardiovascular surgery, in that an anastomosis (the sutured junction between two vessels) reflects more closely the natural compliance of the anatomical vessel. Such simulation of the properties of the natural vessel should help maintain long term patency of the anastomosis after surgery, in contrast to presently used non-elastic sutures which have high long term occlusion rates. A further advantage includes the superior ability of polybutester to maintain strength after gamma-ray sterilization as opposed to many other commonly used elastomeric sutures.

[0014] The stick-slip phenomenon is especially acute when either the suture or the tissue is elastic and when the suture is moving slowly. The problem is accentuated when there are multiple loops of the suture through the tissue (Fig. 1). To overcome this deficiency, the present invention provides a coating to the surface of known polymers. Similarly, these coatings can provide improved performance to metal or ceramic surfaces.

[0015] The present invention thus provides a block copolymer for coating medical or surgical devices comprising an A block having ε-caprolactone linkages and a B block having a poly(alkylene) oxide, characterized in that the A block comprises non-ε-caprolactone linkages subject to hydrolytic degradation in vivo being randomly configured with the ε-caprolactone linkages.

[0016] Preferably, the ABA or AB block copolymers of the invention have an A block comprising linkages of a cyclic ester of an alpha-hydroxy acid and ε-caprolactone, and a B block comprising a poly(alkylene oxide) having a number average molecular weight of 5,000 to 20,000 wherein the ABA or AB block copolymer has a glass transition temperature at or less than 16°C.

[0017] The cyclic ester is preferably glycolide, and the B block is poly(ethylene oxide) or poly-(ethylene oxide-co-propylene oxide).

[0018] Most preferably, the ratio of glycolide to ε-caprolactone components in the A block is within a range of 5 to 50 weight % glycolide and 95 to 50 weight % ε-caprolactone, and the B block comprises up to 95 weight % of said copolymer.

[0019] The invention also provides a medical or surgical device coated with a lubricant manufactured from the ABA copolymer as defined above, and the medical or surgical device being selected from the group consisting of a catheter; surgical needle; bone screw, pin or rod; a surgical clip or staple; and a film.

[0020] Preferably, the surgical suture or ligature is manufactured from a biocompatible polymer selected from the group consisting of nylon, polyester, silk, and polypropylene, and coated with the ABA block copolymer.

[0021] The surgical suture or ligature of the invention may be a monofilament wherein the biocompatible polymer is a poly(ether-co-ester).

[0022] Described are also surgical suture or ligatures having a bioabsorbable coating manufactured from the block copolymer of the invention.

[0023] A number of hydrophobic absorbable coatings are disclosed in printed publications. These coatings were applied primarily for improvement of knot tying characteristics of multifilamentary sutures. The following U.S. Patents are illustrative: 4,791,929, 4,788,979, 4,705,820, 4,624,256, 4,201,216, and 4,994,074; and EP applications 436308, EP 411545, EP 376656.

[0024] One patent for improvement of knot tying characteristics contained a hydrophilic polymer component blended with two hydrophobic components (U.S. 4,027,676).

[0025] Several patents exemplify sutures with absorbable hydrophilic coatings for the primary purpose of improving knot tying characteristics: U.S. 4,857,602, 4,649,920, 4,047,533, 4,043,344. Two patents exemplify hydrophilic non-absorbable coatings to improve wettability and smoothness, GB 1248513, or to provide for controlled release of an antimicrobial agent, U.S. 4,875,479.

[0026] A number of patents disclose the use of non-absorbable hydrophilic coatings for medical articles for the purpose of lubrication: U.S. 5,041,100, 4,976,703, 4,961,954, 4,835,003, 4,801,475, 4,743,673, 4,729,914, 4,666,437, 4,589,873, 4,585,666, 4,487,808, 4,373,009, 4,100,309, 4,459,317, 4,487,808, and 4,729,914. Two additional published patent applications disclose hydrophilic lubricant coatings based on water soluble film forming polymers: EP 14238 and WO 8810284 A1.

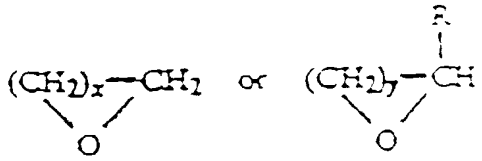
[0027] Several patents disclose the preparation of synthetic absorbable hydrogel polymers. One of these patents, U.S. 4,716,203, discloses the use of a synthetic absorbable hydrogel polymer for the improvement of knot tying characteristics. The remaining patents describe the preparation of synthetic absorbable hydrogels: U.S. Patents 4,942,035, 4,826,945, 4,526,938, 4,452,973, 4,438,253. These patents do not disclose the use of the exemplified materials as suture coatings for tissue drag reduction. It is not necessarily true that a hydrophilic or hydrogel polymers will perform well as a coating for tissue drag reduction, since the coating must possess the characteristics of low friction with tissue

combined with good adherence as is demonstrated when friction does not increase as the material is repeatedly rubbed against tissue.

Summary of the Invention

[0028] The following embodiments more fully describe the invention.

1. A block copolymer for coating medical or surgical devices comprising an A block having ε-caprolactone linkages and a B block having a poly(alkylene) oxide, characterized in that the A block comprises non-ε-caprolactone linkages subject to hydrolytic degradation in vivo being randomly configured with the ε-caprolactone linkages.
2. The copolymer of embodiment 1 wherein the B block is obtained by removing at least one terminal hydroxyl hydrogen from either a homopolymer of ethylene oxide or a copolymer of ethylene oxide and a cyclic ether, and reacting the homopolymer or copolymer with a monomer used to obtain said A block.
3. The copolymer of embodiment 2 wherein the cyclic ether is selected from the group consisting of



wherein x is 1 to 9, y is 1 to 9 and R is a C_1 to C_6 Alkyl group.
4. The copolymer of embodiment 2 wherein said B block is from about 5 to 95 percent by weight of said copolymer.
5. The copolymer of embodiment 4 wherein said B block is from about 20 to 60 percent by weight of said copolymer.
6. The copolymer of embodiment 5 wherein said B block is from about 25 to 45 percent.
7. The copolymer of Claim 2 wherein the number average molecular weight of said B block is from about 4,000 to 30,000.
8. A bioabsorbable copolymer of embodiment 7 wherein the inherent viscosity of the copolymer, as measured at 30°C. for a 0.5% (w/v) solution in chloroform or methylene chloride, is 0.25 to about 1.50 dl/g.
9. A multiblock copolymer as in one of embodiments 1 to 7.
10. A triblock copolymer as in one of embodiments 1 to 7.
11. A diblock copolymer as in one of embodiments 1 to 7.
12. An ABA or AB block copolymer having a (B) block comprising a poly(alkylene oxide) having a number average molecular weight of about 5,000 to 20,000 and an A block comprising a biodegradable random copolymer of (1) the cyclic ester of an alpha-hydroxy acid and (2) ε-caprolactone, wherein the ABA or AB block polymer has a glass transition temperature at or less than 16°C.
13. An ABA block polymer according to embodiment 12 wherein the first cyclic ester is glycolide.
14. The polymer according to embodiment 13 wherein the B block is poly(ethylene oxide) or poly(ethylene oxide-co-propylene oxide).
15. The polymer according to embodiment 13 wherein the poly(alkylene oxide) comprises up to about 95 weight percent and the ratio of glycolide to ε-caprolactone components is within a range of about 5 weight percent glycolide and 95 weight percent ε-caprolactone to about 50 weight percent glycolide and 50 weight percent ε-caprolactone.
16. The polymer according to embodiment 15 wherein said ratio is within a range of about 60 to 90 weight percent ε-caprolactone.
17. The polymer according to embodiment 16 wherein said ratio is within a range of about 80 to 90 weight percent ε-caprolactone.
18. The polymer according to embodiment 17 wherein the ε-caprolactone component is about 85 weight percent.
19. The polymer according to embodiment 15 wherein said poly(alkylene oxide) comprises about 20 to 60 weight percent of the ABA polymer.
20. The polymer according to embodiment 19 wherein said polymer(alkylene oxide) comprises about 25 to 45 weight percent.
21. The polymer according to embodiment 15 wherein the number average molecular weight of said poly(alkylene oxide) is from about 6,000 to 20,000.
22. The polymer according to embodiment 21 wherein the said number average molecular weight of said poly(alkylene oxide) is up to about 14,000.

23. The polymer according to embodiment 22 wherein said number average molecular weight of said poly(alkylene oxide) is from about 8,000 to 14,000.
24. An AB block copolymer according to embodiment 12 wherein the first cyclic ester is glycolide.
25. The polymer according to embodiment 24 wherein the B block is a monomethyl ether of a hydroxyl ended polyethylene oxide.
26. An article of manufacture comprising a lubricant, the lubricant manufactured from the copolymer as in one of embodiments 13 to 23.
27. An article of manufacture comprising a medical or surgical device coated with the lubricant of embodiment 26.
28. The article of embodiment 27 comprising a catheter.
29. The article of embodiment 27 comprising a surgical needle.
30. The article of embodiment 27 comprising a bone screw, pin or rod.
31. The article of embodiment 27 comprising a surgical clip or staple.
32. The article of embodiment 27 comprising a film.
33. An article of manufacture comprising a surgical filamentary device having a bioabsorbable coating according to the claims, the bioabsorbable coating manufactured from the copolymer as in one of embodiments 13 to 23.
34. The article of embodiment 33 wherein the surgical filamentary device is a suture or ligature.
35. The article of embodiment 34 wherein the suture or ligature is manufactured from a biocompatible polymer.
36. The article of embodiment 35 wherein the biocompatible polymer is selected from the group consisting of nylon, polybutester and polypropylene.
37. The article of embodiment 34 wherein the suture or ligature is a monofilament.
38. The article of embodiment 37 wherein said suture or ligature is manufactured from a polybutester.
39. The article of embodiment 34 wherein the suture or ligature is a multifilament.
40. The article of embodiment 39 wherein said suture or ligature is manufactured from a nonabsorbable polymer selected from the group consisting of polyester, nylon and silk.
41. The article of embodiment 33 wherein the surgical filamentary device is a knitted or woven mesh.
42. An article of manufacture comprising a surgical suture or ligature having a bioabsorbable coating, the improvement comprising the bioabsorbable coating according to the invention having a reduced tissue friction, the reduced tissue friction being at least about 10 percent less than an uncoated surgical suture or ligature, and remaining after about 2 to 20 passes through mammalian tissue having a thickness of up to about 2 cm.
43. The article of embodiment 42 wherein the reduced tissue friction is up to about 90 percent less than the uncoated surgical suture or ligature.
44. The article of embodiment 43 wherein the reduced tissue friction is at least about 20 up to about 80 percent less than said uncoated surgical suture or ligature.
45. The article of embodiment 44 wherein the reduced tissue friction is at least about 50 percent less than said uncoated surgical suture or ligature.
46. The article as in one of embodiments 42 to 48 wherein the reduced tissue friction remains after up to about 10 passes through mammalian tissue having a thickness of about 1 cm.
47. The article as in one of embodiments 42 to 48 wherein the suture or ligature is a monofilament.
48. The article of embodiment 47 wherein said suture or ligature is manufactured from a bioabsorbable polymer.
49. The article of embodiment 48 wherein the polymer is a homopolymer.
50. The article of embodiment 49 wherein the homopolymer is polydioxanone.
51. The article of embodiment 48 wherein the polymer is a copolymer.
52. The article of embodiment 51 wherein the copolymer comprises at least one glycolic acid ester linkage.
53. The article of embodiment 52 wherein the copolymer is polyglycolate.

[0029] The surgical filamentary devices of the application, manufactured from a nonabsorbable polymer selected from the group consisting of polybutester, polyester, nylon and silk, may be sterilized by a process comprising:

packaging said suture or ligature in a sealed container that is impervious to microorganisms;
exposing the packaged suture or ligature to a gamma irradiation facility;
irradiating said packaged suture or ligature at at least about 1.5 Mrads; and
removing the irradiated packaged suture or ligature from the gamma irradiation facility.

[0030] The irradiating step is preferably carried out at at least about 2.5 Mrads and up to about 5 Mrads.

Brief Description of the Accompanying Figures

[0031]

Figure 1 shows multiple loops of an elastomeric suture through a wound. Such a technique may be used for many tissues, including vascular tissue.

Figure 2 - Graph of equilibrium water content of copolymer rods immersed in deionized water at 37°C.

Figure 3 shows the apparatus used for measuring friction. A suture is passed through a piece of animal tissue (e.g. ovine aorta or myocardium, or cow tongue) to which a 100g or 200g weight is attached. One end of the suture is fixed, and the other end is attached to a force transducer. The force is measured as the suture moves through the tissue.

Figure 4 - Hysteresis-like curve from Instron testing machine tissue friction test of Size 6/0 polypropylene suture for comparison to Figure 5 as described in Example 5.

Figure 5 - Hysteresis-like curve from Instron testing machine tissue friction test of Size 6/0 polybutester suture coated with the polymer known as example 1N (1 dip) as described in Example 5.

Figure 6 - Graph of coefficient of Friction measurements as described in Example 6 versus the weight percent of PLURONIC™ F-68 (BASF Wyandotte) incorporated in the coating copolymer for polybutester suture coated with copolymers 1J, 1K, 1L, 1M and 1N.

Figure 7 - Graph of coefficient of Friction measurements as described in Example 6 versus equilibrium water content (see Example 3) of coating copolymers for polybutester suture coated with copolymers from Examples 1J, 1K, 1L, 1M and 1N.

Description of the Invention

[0032] The sutures of this invention are composite structures in that they are multilayer materials fabricated by applying a thin layer onto a conventional material that serves as the bulk of the multilayer composite.

[0033] Novel elastomeric sutures provided by this invention are fabricated using a known material for the bulk material and applying a novel thin coating to the fiber made from the bulk material. The bulk material provides mechanical properties suitable to the application, while the novel thin layer must be stable with time and be capable of smooth passage through human or animal tissue. The multilayer structure of the invention permits independent optimization of bulk and tissue response properties.

[0034] This invention also provides a process for the production of said elastomeric sutures. The process comprise the application of a hydrophilic block copolymer to the surface of said elastomeric sutures by contacting said sutures with a solution consisting of a volatile solvent e.g. acetone, ethyl acetate, methylene chloride, methyl ethyl ketone (MEK), and a quantity of said hydrophilic block copolymer. The volatile solvent is allowed to evaporate, leaving a composite structure comprising the bulk polymeric material and a thin layer of said hydrophilic block copolymer.

[0035] Any one of the known materials such as polybutester, polypropylene, silk, catgut, nylon, polyglycolic acid, polyglyconate, stainless steel, cotton, etc. may be used for the bulk material because the process of this invention can proceed without regard for the composition of the bulk material, with the exception that the adhesion of the coating to the surface of the bulk material is affected by the compatibility of the coating copolymers with the bulk material surface. The invention is particularly applicable to polymeric materials which have inadequate frictional properties with tissue, but have useful mechanical properties. For vascular surgery the preferred bulk material is polybutester due to its elastomeric properties.

[0036] In another aspect, this invention provides metallic and inorganic materials modified by the process of this invention in order to equip them with a low friction polymer coating, for example suture needles.

[0037] As a suture or suture-needle coating, the hydrophilic block copolymer coating can be absorbable or nonabsorbable. In certain cases it may be desirable that the hydrophobic block of the copolymer be nonabsorbable where long term surface hydrophilicity is needed. It may also be advantageous to provide a non-absorbable coating with an absorbable overcoating to provide for short term lubricity as well as specific long term surface properties. Since in certain cases, such as sutures, the reduction of friction between the suture material and tissue is required only during the surgical procedure, and since the compatibility of the bulk material with tissue is well established for the commercial sutures of interest, the preferred coating is an absorbable hydrophilic block copolymer. Absorbable coatings are also advantageous since they would present no long term risks should they be ablated during the surgical procedure.

[0038] The absorbable block copolymers exemplified in this invention consist of at least one hydrophilic block and at least one hydrophobic block. Said hydrophobic blocks are hydrolyzable under in-vivo conditions. The term "hydrophobic blocks", as used in describing this invention, refers to blocks that are not normally water soluble and absorb relatively low amounts of water, i.e. less than 10% by weight. The hydrophilic blocks, when not covalently bound to the hydrolyzable hydrophobic blocks are normally capable of being dissolved by body fluids. When covalently bound to the

hydrophilic block, the hydrolyzable hydrophobic block provides a mechanism for retaining the hydrophilic block on the surface of the bulk material for the required period of time. The hydrolyzable hydrophobic block provides sufficient compatibility with the bulk material surface to resist ablation and diminution of lubricating properties during the surgical procedure. The chemical composition selected for the hydrolyzable hydrophobic block depends on the chemical nature of the bulk material surface and must be designed to provide adequate adhesion between the coating and the bulk material. A further advantage of this invention is the flexibility of design of the hydrolyzable hydrophobic block. The proper design of the hydrolyzable hydrophobic block eliminates the need for chemical modification of the bulk material surface as is often required in prior-art coating systems to provide adequate adhesion of a coating to a bulk material.

[0039] The hydrolyzable hydrophobic blocks of the current invention comprise non-ε-caprolactone linkages subject to hydrolytic degradation in vivo being randomly configured with ε-caprolactone linkages. The copolymers are formed from ε-caprolactone and monomers selected from the group consisting of:

glycolide, l-lactide, d,l-lactide, d-lactide, meso-lactide, trimethylene carbonate, 4,4-dimethyl-1,3-dioxan-2-one, p-dioxanone, dioxepanone, δ-valerolactone, β-butyrolactone, ε-decalactone, 2,5-diketomorpholine, pivalolactone, α,α-diethylpropiolactone, 6,8-dioxabicyclooctan-7-one, ethylene carbonate, ethylene oxalate, 3-methyl-1,4-dioxane-2,5-dione, 3,3-dimethyl-1,4-dioxane-2,5-dione, and other subtituted glycolides, and substituted lactides. Other cyclic esters described in the art can also be employed within the scope of this invention.

[0040] The hydrophilic blocks having poly(alkylene)oxide of the current invention can be selected from the group consisting of: polyoxyethylene, and polyoxyethylene/polyoxypropylene block copolymers. The methods of preparation of the hydrophilic block copolymers of this invention are known in the prior art.

[0041] In a preferred embodiment of the hydrophilic block copolymer of this invention, the hydrophilic blocks are comprised of polyoxyethylene or polyoxyethylene/polyoxypropylene block copolymers, and the hydrolyzable hydrophobic blocks are comprised of a copolymer of ε-caprolactone and glycolide and the substrate suture material is polybutester.

[0042] In another preferred embodiment of the hydrophilic block copolymer of this invention the hydrophilic blocks are comprised of polyoxyethylene or polyoxyethylene/polyoxypropylene copolymer, and the hydrolyzable hydrophobic block is comprised of a copolymer of glycolide and trimethylene carbonate and the substrate suture material is polyglycolate.

Measurement of Frictional Properties

[0043] Frictional tests using sheep aorta or myocardium or cow tongue provide a convenient assay of tissue drag. Such studies are also directly relevant to medical or veterinary applications in contrast to tests done with steel surfaces or rubber. It is considered that the surface treatment procedures suitable for the reduction of friction in animal tissue are also appropriate for the optimization of sutures for general surgery.

[0044] Other aspects of the present invention, and modifications and variations thereto, will become apparent to those skilled in the art on reading this invention, and all such other aspects and modifications and variations are to be considered to be included within the scope of the present invention.

EXAMPLES

Example 1: Preparation of Coating Polymers

Purification of Polyethylene Glycol (Polyoxyethylene) or PLURONIC™ F-68 (Polyoxyethylene/polyoxypropylene block copolymer from BASF Wyandotte):

[0045] The material to be purified is dissolved in methanol at a concentration of 10 % w/v. The solution is then freed of residues by slowly passing the solution through a methanol conditioned mixed bed anionic and cationic exchange resin (TMD8, Alcoa Separations Technology Inc., IL, U.S.A.). The methanol is then removed on a rotary evaporator. Prior to polymerization, the desired amount of purified diol is dried in a vacuum oven for 18 hours at 90°C and <1 mm Hg.

Polymer Synthesis:

[0046] The desired amounts of cyclic ester or carbonate monomer(s) and polyethylene glycol or PLURONIC® F-68 were charged to a flask and melted under nitrogen. Catalyst was then added and the contents were charged to a heated, nitrogen purged reactor. The mixture is stirred at the polymerization temperature for a specified period of time.

The polymer was discharged from the reactor and dried in a vacuum oven for 18 hours at 70-80°C and <1 mm Hg. Specific examples of polymers produced by this procedure are given in Table 1.

Example 2

ε-Caprolactone/trimethylene carbonate/polyethylene glycol pentablock polymer

[0047] Purified polyethylene glycol, 8000 molecular weight, (PEG 8000, 10.00g), trimethylene carbonate, (TMC, 27.00g), and stannous octoate (3.3 mg, 0.001 mole percent based on TMC plus ε-Caprolactone) were melted together under nitrogen. The mixture was charged to a preheated, nitrogen purged stirred reactor. The contents were stirred at 185°C for 4 hours 30 minutes. ε-Caprolactone (Cap 63.00g) was then charged to the reactor and the contents were stirred at 185°C for an additional 1 hour 25 minutes. The polymer was discharged from the reactor and dried in a vacuum oven for 18 hours at 75°C and <1 mm Hg. The polymer had an inherent viscosity of 1.12 dL/g in chloroform at 30°C at a concentration of 0.5 g/dL. The composition was 66.9/23.0/10.1 weight percent Cap/TMC/PEO as measured by 1H-NMR spectroscopy.

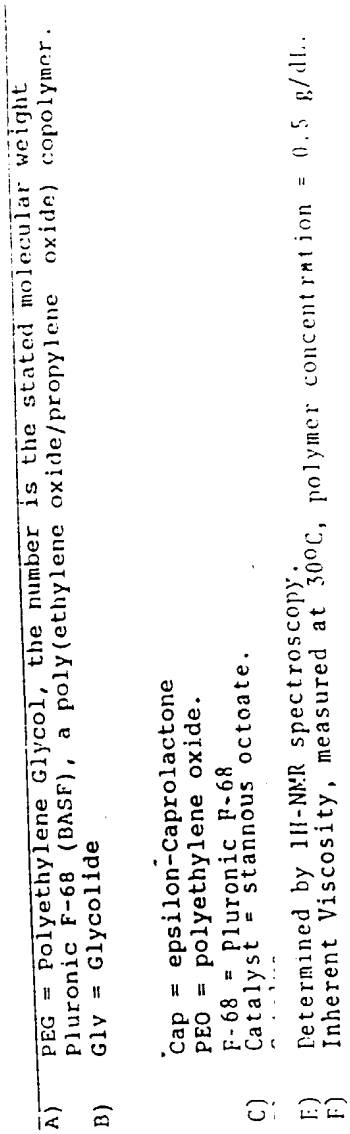
Example 3

Water Uptake of Various Coating Polymers

[0048] Water uptake experiments were carried out on injection molded rods with a diameter of 1/8" and a length of 1-2 cm. These rods were fabricated from polymers from Example 1. The samples were immersed in deionized water or phosphate buffered saline at pH 7.4. Periodically a sample was removed, wiped free of surface moisture and weighed. This was continued until an equilibrium weight was obtained. Equilibrium water content values are summarized in Table 2. In cases where the sample became badly fragmented as a result of swelling, the moisture content was determined by weight loss after drying. The data for water uptake is

TABLE 1

Example	Polyalkylene oxide[A] (g)	Endblocks[B] (g)	Catalyst[C] mg (mole %)	Polymerization Temp (C)	Time (hr:min)	Polymer Composition[D] (weight percent)	IV[E] (solvent)
1G	PEG 8000 (25.00)	Cap/Gly (191.25/33.75)	55.8 (0.007)	180	4:30	Cap/Gly/PEO (75.8/13.9/10.3)	1.07(CHCl3)
1H	PEG 8000 (30.00)	Cap/Gly (59.50/10.50)	17.3 (0.007)	180	4:30	Cap/Gly/PEO (56.4/11.1/32.5)	0.54(CHCl3)
1J	F-68 (25.00)	Cap/Gly (191.25/33.75)	55.8 (0.007)	180	4:30	Cap/Gly/F-68 (75.9/13.8/10.3)	1.08(CHCl3)
1K	F-68 (37.50)	Cap/Gly (180.62/37.50)	52.6 (0.007)	180	4:30	Cap/Gly/F-68 (72.2/13.0/14.8)	0.89(CHCl3)
1L	F-68 (50.00)	Cap/Gly (170.00/30.00)	49.6 (0.007)	180	4:30	Cap/Gly/F-68 (67.5/13.0/19.5)	0.76(CHCl3)
1M	F-68 (30.00)	Cap/Gly (59.50/10.50)	17.3 (0.007)	180	4:30	Cap/Gly/F-68 (60.6/10.3/29.1)	0.56(CHCl3)
1N	F-68 (40.00)	Cap/Gly (51.00/9.00)	14.9 (0.007)	180	4:30	Cap/Gly/F-68 (47.8/10.3/41.9)	0.46(CHCl3)



summarized in Table 2. Water uptake data for Examples 1J, 1K, 1L, 1M and 1N are shown graphically in Figure 2.

Example 4

Coating Procedure

[0049] Polymer samples from Example 1 were dissolved at a 5 g/dL concentration in acetone (or in methylene chloride if the polymers were not acetone soluble). Coatings were applied to polybutester sutures by hand-dipping lengths of size 6/0 polybutester sutures in the solutions. The hand-dipping procedure consisted of passing the suture through the solution by pulling one end of the strand while holding a portion of the strand in the solution using a ceramic guide rod with a grooved tip. Up to three passes through the solution were used to apply coatings of increasing thickness. The actual coating level was not measured.

Table 2

Water Uptake			
Polymer from Example Number	Temperature (C)	Swelling Medium	EWC[A]
1G	RT	DI H2O	20
	37	DI H2O	24
1J	RT	DI H2O	14
	37	DI H2O	16
1K	RT	DI H2O	24
	37	DI H2O	26
1L	RT	DI H2O	71
	37	DI H2O	58
	RT	PBS	48
	37	PBS	41
1M	37	DI H2O	101
1N	37	DI H2O	158

A) Equilibrium water content = 100 * (wt. hydrated - wt. dry)/(wt. dry) . See Example 3.

Example 5

Tissue Drag Measurement

[0050] Tissue drag was determined by measuring the force required to draw a suture through a piece of cow tongue using an Instron testing machine. Suture specimens were prepared as described in Example 4. All samples in this Example were size 6/0 and had the same size needle. Coated polybutester sutures had a TE-1 needle and an uncoated comparison polypropylene suture (PROLENE®) had the closest equivalent needle (C-1). A small piece of cow tongue was cut into approximately a 1 cm cube. The tongue was kept moistened at all times with Dulbecco's Phosphate Buffered Saline (Cat. No. 310-4190 AK). A 100 g weight was attached to the tongue cube. The needle was then passed through the tissue. One end of of the suture was affixed to a stationary clamp on the Instron machine. The other end of the suture was clamped to the load cell, so that the tissue and the attached weight hung free. Figure 3 shows a schematic of the apparatus for measuring tissue drag. The Instron was set to cycle five times over a 8.89 cm (3.5") distance at a speed of 25.4 cm/min (10 inches/minute). A full scale load of 200 grams was used and the data was collected on a strip chart recorder with a chart speed of 25.4 cm/min (10 inches/minute). The strip chart was also set to cycle with the Instron crosshead to produce a "hysteresis-like curve" with forces associated with the ascending and descending crosshead movement.

[0051] To interpret the data, the difference between the average maximum (ascending crosshead) force and average minimum (descending crosshead) force was calculated. Four specimens of each suture sample were tested using the same tissue cube. An uncoated comparison suture (PROLENE® polypropylene suture with a C-1 needle) was then tested in the same manner. The values for the force differences of the four test specimens were averaged and divided by the force difference for the comparison suture and a relative value was determined. This value was called the "Friction Index". Samples with more frictional resistance than the comparison suture had friction index values greater than 1, and those with lower frictional resistance than the comparison suture had friction index values less than 1. Figures 4 and 5 show typical strip chart traces for the polypropylene comparison sample and for polybutester coated with the polymer from example 1N. See Table 3 for the Friction Index results of this testing. Some of the Friction Index values in Table 3 appear to show an increase with increased coating level (more dips). This increase may be due to increased surface roughness (or unevenness) of the thicker coatings.

Example 6

Coefficient of Friction

[0052] Tissue drag was also determined by measuring the force required to draw a suture through a piece of sheep heart muscle using an Instron testing machine. The heart tissue was taken from the left ventricular wall. The tissue was kept moist throughout the experiment with 0.9 g/dL $NaCl/H_2O$ solution. The test procedure was similar to that described in Example 5 with the exceptions that an eyed needle (Davis & Geck TS-2, 41 cm) was used rather than an attached needle and the attached weight was 200 g. In this example, the coefficient of friction (μ) was calculated using the following formula:

$$\mu = F/N$$

where

F = ascending force - descending force

N = ascending force + descending force

[0053] In this test, the value for μ was determined for each cycle of the test (a cycle is defined as one ascending pass and one descending pass) and a total of three cycles was run for each sample.

[0054] This test was used to study the effect of the degree of hydrophilicity on the coefficient of friction of the coated suture. Samples containing PLURONIC® F-68 (F-68) as the hydrophilic block - samples 1J, 1K, 1L, 1M and 1N - were used in this example. The degree of hydrophilicity was determined in two ways: the percent of F-68 (see Example 1) and the equilibrium moisture uptake (see Example 3). The relationships of μ versus the F-68 content of the coating polymers and versus the water uptake of the coating polymers are shown graphically in Figures 6 and 7 for coating polymers 1J through 1N. In these graphs, the values plotted for 0% F-68 and 0% water uptake are the values for uncoated polybutester. If a copolymer of the composition of the hydrolyzable hydrophobic block were used for the 0% F-68 data point, the value for coefficient of friction would not be expected to be significantly less than uncoated polybutester. Also, the value for the coefficient of friction for sample 1N was calculated from data obtained using the Example 5 method. Higher concentrations of F-68 would be more hydrophilic than

TABLE 3

Friction Index Testing Results			
Example Uncoated	Solvent[A]	No. Dips[B]	Friction Index[C]
1M	A	1	0.684
		2	0.703
		3	0.870
1N	A	1	0.500
		3	0.468
1H	A	1	0.484
		3	0.441

A) M = Methylene Chloride, A = Acetone
B) Number of times the suture was dipped, see example 4
C) See example 5 for explanation of friction index

the coatings in Figures 6 and 7, and may provide superior lubricity, but higher F-68 levels may result in the loss of coating durability. A coating of pure F-68 would be expected to be quickly removed from the suture surface after contacting the moist tissue.

Example 7

Radiation Effect on Tissue Drag

[0055] Size 6/0 polybutester suture was coated with the polymer from Example 1M. The samples were coated from a 3.5 g/dL acetone solution using a capillary coating machine. The coating level was 0.35% by weight, measured gravimetrically after stripping off the coating with acetone. Test sutures were made by cutting the fiber to length and attaching TE-1 needles. Some of the samples were then packaged and sterilized by γ-irradiation at 2.5 Mrad as is done for commercial NOVAFIL® suture. Other samples were packaged, but not sterilized. Tissue drag was measured for both sterile and nonsterile samples as described in Example 5. The friction index values were 0.83 for the non-sterile and 0.85 for the sterile suture. This is not considered a significant difference in friction index.

Claims

1. A block copolymer for coating medical or surgical devices comprising an A block having ε-caprolactone linkages and a B block having a poly(alkylene) oxide, characterized in that the A block comprises non-ε-caprolactone linkages subject to hydrolytic degradation in vivo being randomly configured with the ε-caprolactone linkages.

2. An ABA or AB block copolymer of Claim 1 having an A block comprising linkages of a cyclic ester of an alpha-hydroxy acid and ε-caprolactone, and a B block comprising a poly(alkylene oxide) having a number average molecular weight of 5,000 to 20,000 wherein the ABA or AB block copolymer has a glass transition temperature at or less than 16°C.

3. The copolymer of Claim 2 wherein the cyclic ester is glycolide, and the B block is poly(ethylene oxide) or poly-(ethylene oxide-co-propylene oxide).

4. The copolymer of Claim 2 wherein the cyclic ester is glycolide.

5. The copolymer of Claim 2 wherein the B-block is poly(ethylene oxide) or poly-(ethylene oxide-co-propylene oxide).

6. The copolymer of any one of Claims 3 or 4 wherein the ratio of glycolide to ε-caprolactone components in the A block is within a range of 5 to 50 weight % glycolide and 95 to 50 weight % ε-caprolactone, and the B block comprises up to 95 weight % of said copolymer.

7. A medical or surgical device coated with a lubricant manufactured from the ABA copolymer as in one of Claims 2 to 6, and the medical or surgical device selected from the group consisting of a catheter; surgical needle; bone screw, pin or rod; a surgical clip or staple; and a film.

8. A surgical suture or ligature manufactured from a biocompatible polymer selected from the group consisting of nylon, polyester, silk, and polypropylene, and coated with the ABA block copolymer as in one of Claims 2 to 6.

9. The surgical suture or ligature of Claim 8 as a monofilament wherein the biocompatible polymer is a poly(ether-co-ester).

10. A surgical suture or ligature having a bioabsorbable coating manufactured from the block copolymer as in one of Claims 1 to 6.

Patentansprüche

1. Blockcopolymer zum Beschichten von medizinischen oder chirurgischen Vorrichtungen, das einen A-Block umfasst, der ε-Caprolactonverknüpfungen aufweist, sowie einen B-Block, der ein Polyalkylenoxid aufweist, dadurch gekennzeichnet, dass der A-Block einem hydrolytischen Abbau in vivo ausgesetzte Verknüpfungen aufweist, die keine ε-Caprolactonverknüpfungen sind und statistisch mit den ε-Caprolactonverknüpfungen angeordnet sind.

2. ABA- oder AB-Blockcopolymer nach Anspruch 1, das einen A-Block aufweist, der Verknüpfungen eines cyclischen Esters einer alpha-Hydroxysäure und eines ε-Caprolactons umfasst, und das einen B-Block aufweist, der ein Polyalkylenoxid umfasst, das ein Molekulargewicht-Zahlenmittel von 5000 bis 20000 aufweist, wobei das ABA- oder

AB-Blockcopolymer eine Glasübergangstemperatur von 16 °C oder weniger besitzt.

3. Copolymer nach Anspruch 2, wobei der cyclische Ester Glykolid ist und der B-Block Polyethylenoxid oder Polyethylenoxid-Copropylenoxid ist.

4. Copolymer nach Anspruch 2, wobei der cyclische Ester Glykolid ist.

5. Copolymer nach Anspruch 2, wobei der B-Block Polyethylenoxid oder Polyethylenoxid-Copropylenoxid ist.

6. Copolymer nach einem der Ansprüche 3 oder 4, wobei das Verhältnis der Glykolidkomponente zu der ε-Caprolactonkomponente in dem A-Block innerhalb eines Bereichs von 5 bis 50 Gew.-% Glykolid und 95 bis 50 Gew.-% ε-Caprolacton ist, und der B-Block bis zu 95 Gew.-% des Copolymers umfasst.

7. Medizinische Vorrichtung oder Operationsvorrichtung, die mit einem Gleitmittel beschichtet ist, das aus dem ABA-Copolymer nach einem der Ansprüche 2 bis 6 hergestellt ist, und die medizinische Vorrichtung oder die Operationsvorrichtung, die ausgewählt ist aus der Gruppe, bestehend aus einem Katheter; einer Operationsnadel; einer Knochenschraube, einem Knochenstift oder einer Knochenstange; einer Operationsklammer oder Operationsheftklammer; und einem Film.

8. Chirurgisches Nahtmaterial oder chirurgischer Faden, hergestellt aus einem bioverträglichen oder körperverträglichen Polymer, das ausgewählt ist aus einer Gruppe, bestehend aus Nylon, Polyester, Seide und Polypropylen, und das beschichtet ist mit dem ABA-Blockcopolymer nach einem der Ansprüche 2 bis 6.

9. Chirurgisches Nahtmaterial oder chirurgischer Faden nach Anspruch 8 als ein Monofilament, wobei das bioverträgliche oder körperverträgliche Polymer ein Polyether-Coester ist.

10. Chirurgisches Nahtmaterial oder chirurgischer Faden, der eine bioaufnahmefähige Beschichtung aufweist, die aus dem Blockcopolymer nach einem der Ansprüche 1 bis 6 hergestellt ist.

Revendications

1. Copolymère séquencé pour le revêtement de dispositifs médicaux ou chirurgicaux, comprenant une séquence A comportant des liaisons ε-caprolactone, et une séquence B à groupe polyoxyalkylène, caractérisé en ce que la séquence A comprend des liaisons qui ne soient pas des liaisons que ε-caprolactone sujettes à une dégradation hydrolytique in vivo, configurées de manière aléatoire avec les liaisons ε-caprolactone.

2. Copolymère séquencé ABA ou AB selon la revendication 1, comportant une séquence A comprenant des liaisons dérivées d'un ester cyclique d'un acide α-hydroxylé et d'ε-caprolactone, et une séquence B comprenant un groupe polyoxyalkylène ayant un poids moléculaire moyen en nombre de 5 000 à 20 000, le copolymère séquencé ABA ou AB ayant une température de transition vitreuse de 16 °C ou moins.

3. Copolymère selon la revendication 2, dans lequel l'ester cyclique est un glycolide, et la séquence B est un groupe poly(oxyde d'éthylène) ou poly-(oxyde d'éthylène-co-oxyde de propylène).

4. Copolymère selon la revendication 2, dans lequel l'ester cyclique est un glycolide.

5. Copolymère selon la revendication 2, dans lequel la séquence B est un groupe poly(oxyde d'éthylène) ou poly(oxyde d'éthylène-co-oxyde de propylène).

6. Copolymère selon la revendication 3 ou 4, dans lequel le rapport des composants dérivés de glycolide et d'ε-caprolactone dans la séquence A, est de 5 à 50 % en poids de glycolide et de 95 à 50 % en poids d'ε-caprolactone, et la séquence B comprend jusqu'à 95 % en poids dudit copolymère.

7. Dispositif médical ou chirurgical revêtu d'un lubrifiant, fabriqué à partir du copolymère ABA selon l'une des revendications 2 à 6, et le dispositif médical ou chirurgical est choisi parmi un cathéter ; une aiguille chirurgicale ; une vis, une broche ou une tige pour os ; une pince ou une agrafe chirurgicale ; et un film.

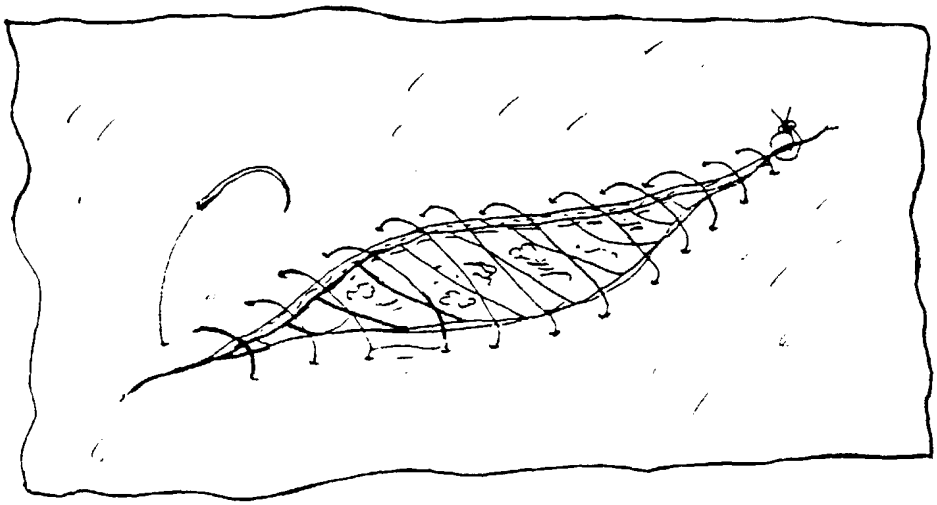
8. Suture ou ligature chirurgicale fabriquée à partir d'un polymère biocompatible choisi parmi le Nylon, un polyester,

la soie et le polypropylène, et revêtue du copolymère séquencé ABA selon l'une des revendications 2 à 6.

9. Suture ou ligature chirurgicale selon la revendication 8 sous forme d'un monofilament dans lequel le polymère biocompatible est un poly(éther-co-ester).

10. Suture ou ligature chirurgicale comportant un revêtement biorésorbable produit à partir du copolymère séquencé selon l'une des revendications 1 à 6.

FIG. 1 (PRIOR ART)



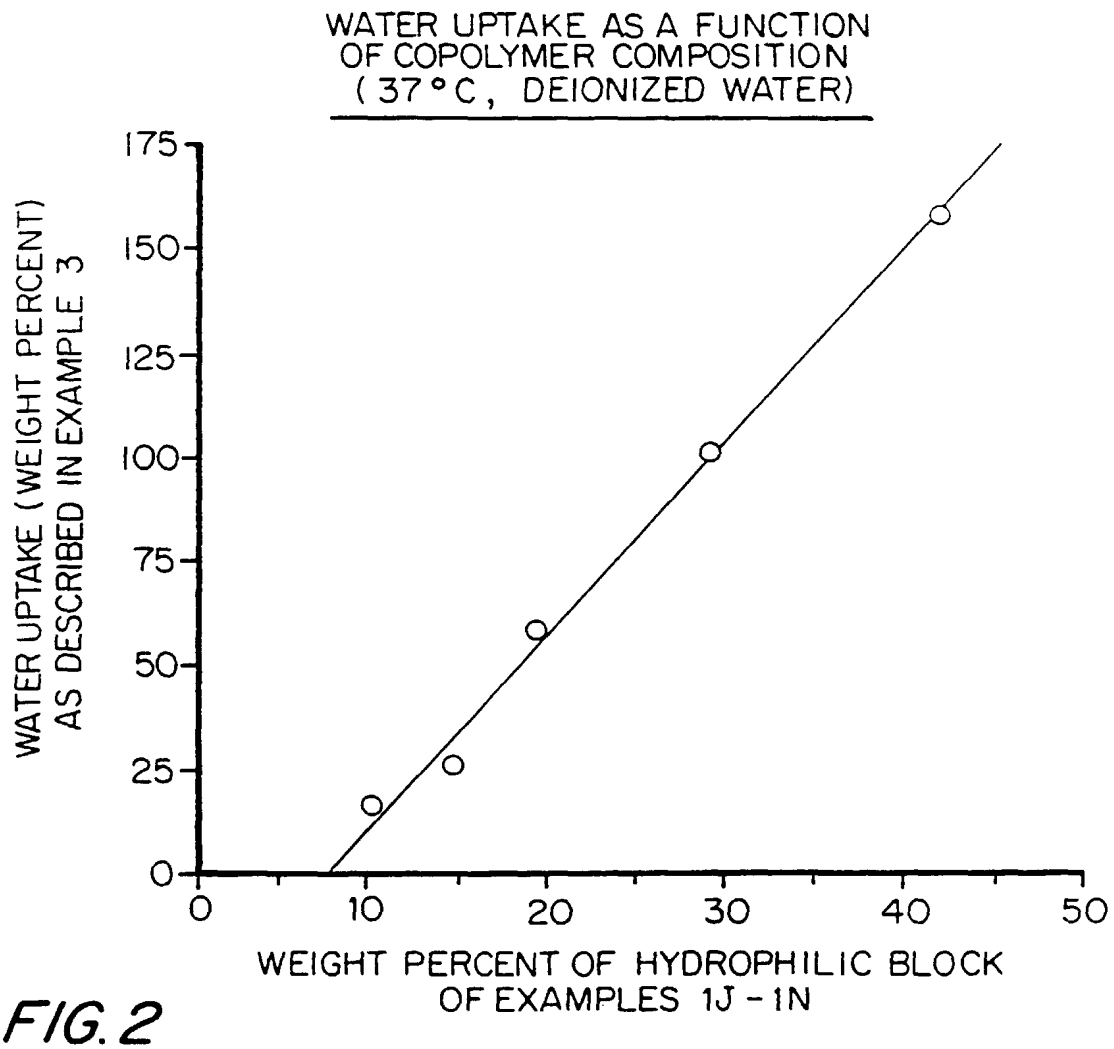


FIG. 2

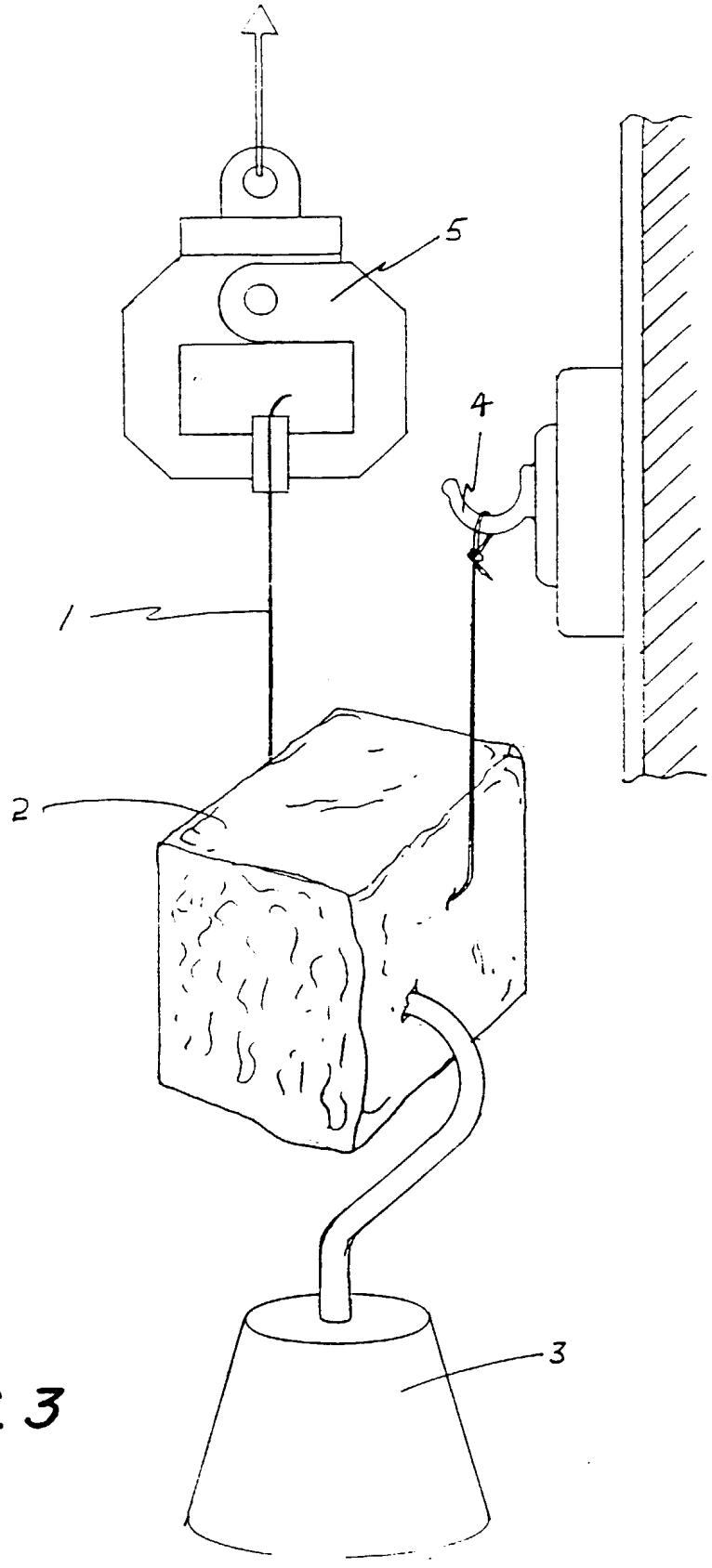


FIG. 3

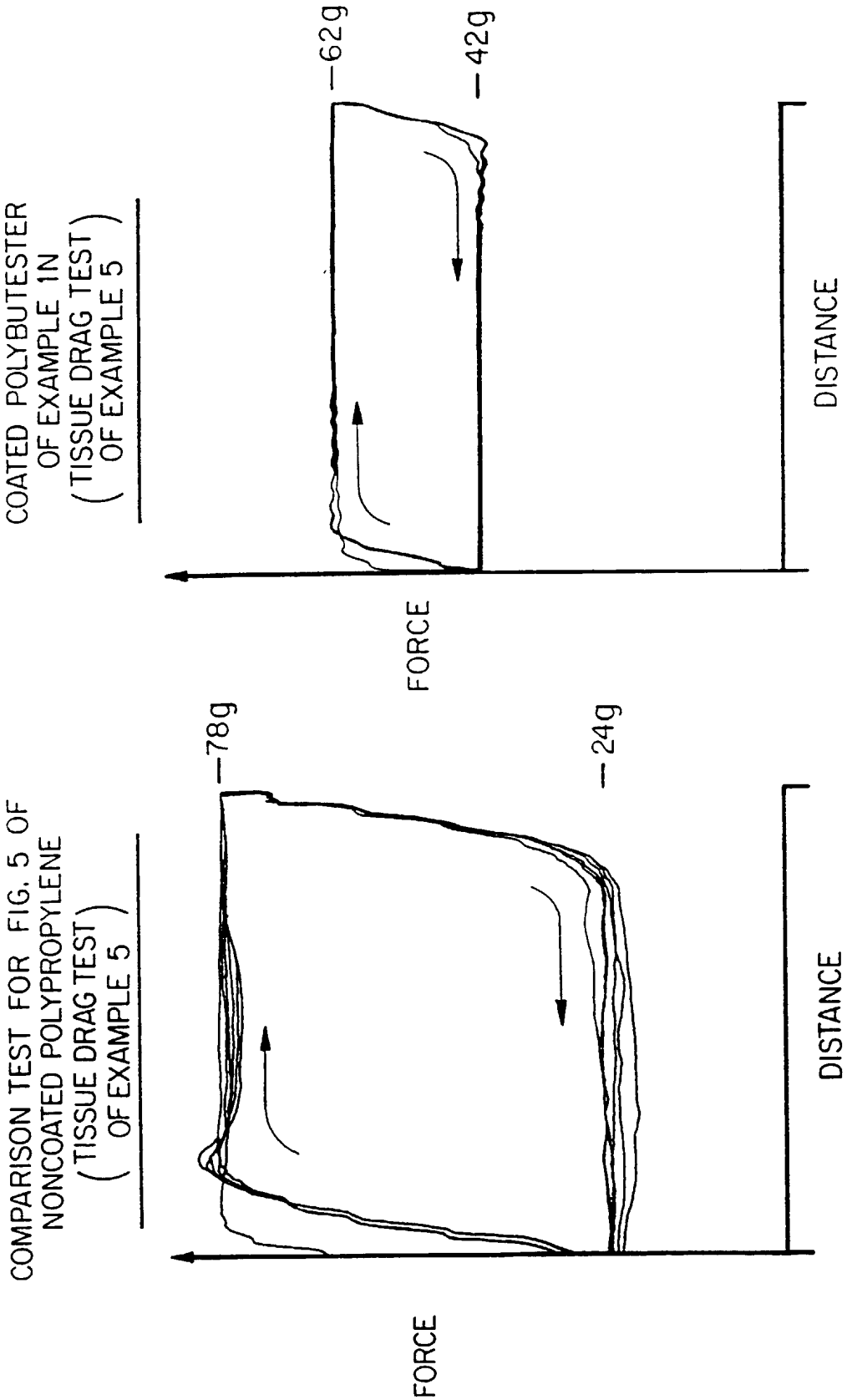

COMPARISON TEST FOR FIG. 5 OF NONCOATED POLYPROPYLENE (TISSUE DRAG TEST OF EXAMPLE 5)
78g
24g
FORCE
DISTANCE
COATED POLYBUTESTER OF EXAMPLE 1N (TISSUE DRAG TEST OF EXAMPLE 5)
62g
42g
FORCE
DISTANCE

FIG. 4

FIG. 5

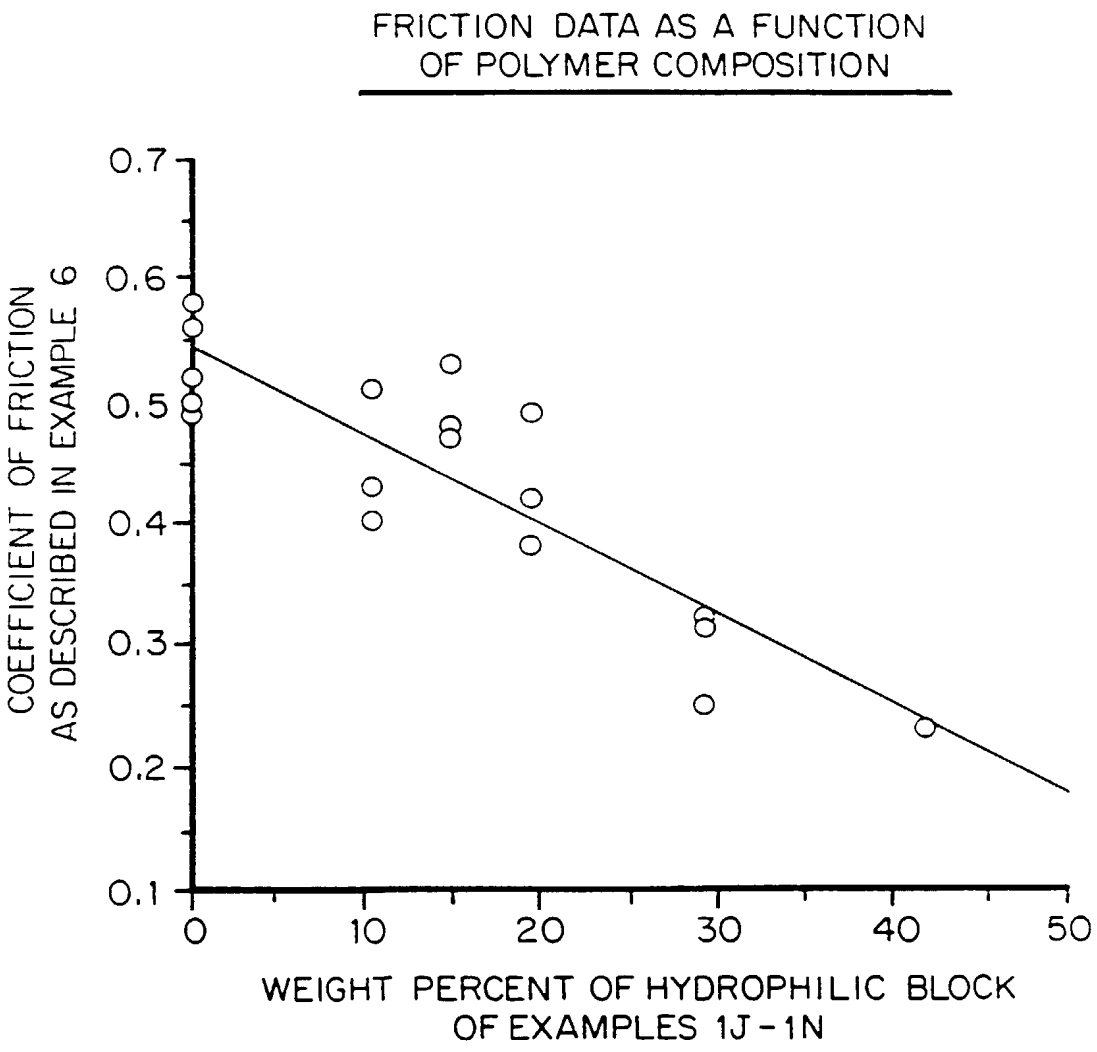

FRICTION DATA AS A FUNCTION
OF POLYMER COMPOSITION
COEFFICIENT OF FRICTION
AS DESCRIBED IN EXAMPLE 6
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10
20
30
40
50
WEIGHT PERCENT OF HYDROPHILIC BLOCK
OF EXAMPLES 1J - 1N

FIG. 6

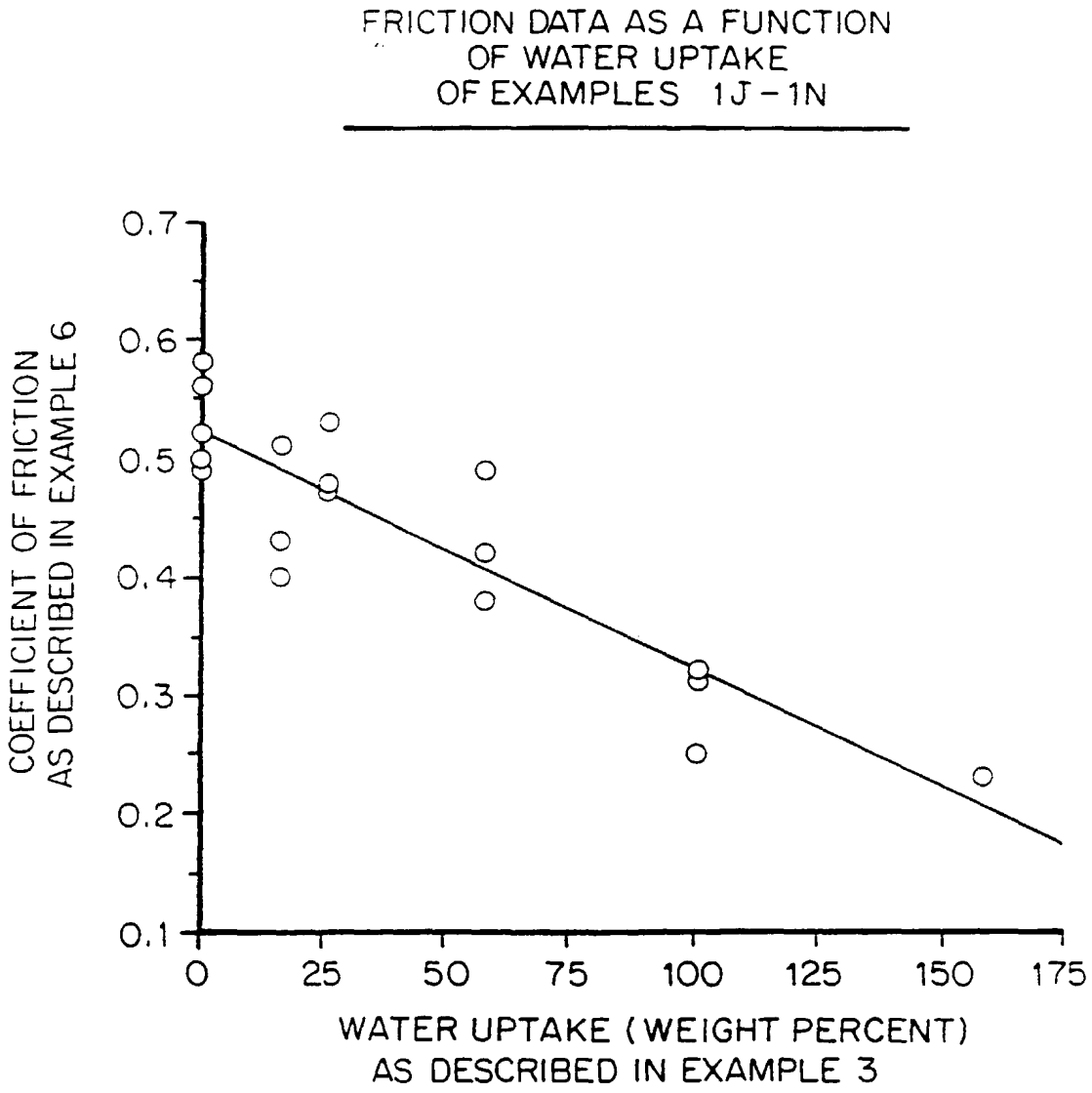

FRICTION DATA AS A FUNCTION
OF WATER UPTAKE
OF EXAMPLES 1J - 1N
COEFFICIENT OF FRICTION
AS DESCRIBED IN EXAMPLE 6
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
25
50
75
100
125
150
175
WATER UPTAKE (WEIGHT PERCENT)
AS DESCRIBED IN EXAMPLE 3

FIG. 7